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THE BIRTH CONTROL PILL

Norethynodrel with ethynylestradiol 3-methyl ether (Enovid - Searle) and norethindrone (Norlutin - Parke, Davis) were approved by the Food and Drug Administration in 1957 for prescription sale as oral progestins. Enovid has now been approved for prescription sale as an oral contraceptive, making it the first oral birth-control preparation to be marketed in this country. Apparently Parke, Davis has not applied for similar approval for Norlutin. If it does, such approval would probably be granted, since the two compounds are similar in their actions.

When dosage is begun in the late menstrual phase and continued through the preovulatory and ovulatory phases of the cycle, both compounds inhibit ovulation by suppressing the gonadotrophic function of the anterior pituitary. Since both compounds have estrogenic as well as progestational effect, they provoke endometrial withdrawal bleeding three to eight days after discontinuance. Extensive investigations, in some instances for about four years, have shown that when properly used, these two oral progestins are at least as effective as the condom and the diaphragm in preventing conception.

DOSAGE - "Proper use" consists of taking 10 mg. daily for 20 days beginning with the fifth day of the menstrual cycle. In three to eight days following the last dose, withdrawal bleeding appears. The patient then recommences the 20 days of drug therapy on the fifth day after the onset of bleeding, maintaining this regimen indefinitely. About 70 per cent of patients report diminished menstrual flow, 15 per cent increased flow, and 15 per cent no change in flow. Infrequently, and in an occasional cycle, a patient will not develop withdrawal bleeding; therefore patients are carefully instructed to reinstitute the 20 days of therapy after an interval of 10 days in the absence of menstrual-like bleeding. (If use of the drug has been irregular during the 20 days and there is any reason to believe that pregnancy has occurred, further medication should be postponed because of the possibility of masculinizing effects of the drug on the female fetus.) Enovid and Norlutin have been given to lactating women as contraceptives without observed diminution of milk or adverse effect on their babies.

SIDE EFFECTS AND COST - The chief practical objections of patients to both Enovid and Norlutin are their occasional side effects and their expense, and many women discontinue their use for either or both reasons. Ten mg. of either

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drug retails for 60¢ to 70¢ so that a month's supply costs $12 to $14. Approximately 15 per cent of patients will develop objectionable, though not dangerous, side effects. Many of these side effects disappear after a time if the patient continues the drug. Among the more prominent side effects are nausea, headache, chloasma, acne, breakthrough bleeding, weight gain and, infrequently, loss of libido. Nausea is often diminished if the drug is taken in the evening. All of the side effects are reversible, disappearing on discontinuance of the drug. Breakthrough bleeding frequently disappears if the dose is doubled for a few days.

Follow-up studies, including physical examinations, endometrial biopsies, cephalin flocculation tests, tests for urinary 17-ketosteroids, and complete blood counts, have not shown any long-term endocrine or other somatic effects from either drug. The longest period of use reported is 44 months. Several patients have discontinued the drug after a year or more and have achieved desired pregnancies. No one can yet prove, however, that five or ten years of continuous use will not result in premature decline of ovarian function.

In summary, Enovid is an effective oral contraceptive when used properly. Minor side effects have been noted in about 15 per cent of patients, but to date no major side effects have appeared. Since the average period of use has been relatively short, however, no physician can feel completely confident that long-term use will prove safe for all patients. It is advisable that women using Enovid remain under medical supervision.

PROVERA

Medroxyprogesterone acetate (Provera - Upjohn), a new oral progestational agent, is being promoted for use in menstrual disturbances and in threatened and habitual abortion. It is a potent steroid with no estrogenic or androgenic effects in the conventional animal assays. Like norethynodrel with ethynylestradiol 3-methyl ether (Enovid - Searle) and norethindrone (Norlutin - Parke, Davis) (see The Medical Letter, 2: 7, Jan. 22, 1960), Provera is effective in the treatment of amenorrhea, and in conjunction with estrogens, it can be used to control abnormal uterine bleeding.

A dosage of 2.5 mg. a day for five days produces withdrawal bleeding in women who have adequate estrogenic function or who have been primed with estrogen (R. B. Greenblatt and W. E. Barfield, Southern Med. J., 52: 345, 1959). Since, like progesterone itself, Provera lacks estrogenic effect, it can be used to test for the presence of estrogenic function in amenorrhea.

HABITUAL AND THREATENED ABORTION - The effectiveness of Provera in preventing threatened abortions in humans has yet to be established. It has been shown that the drug helps maintain pregnancy in animals oophorectomized in the second half of pregnancy, but such experiments have no clinical counterpart; oophorectomy in women in the second half of pregnancy does not harm the fetus. Despite reports to the contrary, it is not certain that progesterone deficiency is an important cause of fetal loss, or that supplying progestins reduces fetal loss significantly in humans.

The most serious contraindication to the use of progestational drugs to maintain pregnancy is their occasional masculinizing effect on the fetus. Provera has been free of masculinizing effects in conventional tests in animals, but when it is given to rats during pregnancy it does produce masculinization in female offspring. It will not necessarily have the same effect in humans, but past experience with progestational compounds indicates the need for caution. Provera (like Enovid and Norlutin) should be used in pregnancy only with full understanding that some risk is being taken for a questionable advantage. If a trial of Provera or another progestin is considered imperative, it is best to restrict its use to the second and third trimesters, when there is no longer a risk that it will affect labioscrotal fusion. (Recent reports on virilizing changes caused by progestational agents include M. M. Grumbach, et al., J. Clin. Endocrinology, 19: 1369, 1959; and L. Wilkins, JAMA, 172: 1028, 1960.)

MAN-TAN AND OTHER CHEMICAL SKIN-TANNING PREPARATIONS

To judge from the mail coming into the Medical Letter office, and from full-page advertisements in the public press addressed to physicians, many doctors are being asked about the new chemical tanning preparations now being promoted for use as a substitute for a sun-tan. These preparations do "tan" the skin, the color appearing in about six hours and gradually wearing off in the course of several days. The manufacturer of the leading product of this kind, Man-Tan, recommends three or four applications on the first day of use, with a single daily application thereafter to maintain the color.

Whether the look of a genuine tan is obtained with Man-Tan or some similar preparation is a matter partly of individual skin reaction and partly of individual taste. Both color and intensity vary from person to person; some like the results, others get a yellowish tint which they find unattractive. The user would be well advised to try the preparation on a well-covered area before putting it on his face.

THE ACTIVE AGENT - All of the preparations contain dihydroxyacetone, which produces the color change in the keratin layer of the epidermis. Dihydroxyacetone is a normal product of body metabolism, occurring in the Krebs cycle, and it is non-toxic and non-allergenic. The commercial tanning preparations, however, contain other ingredients besides dihydroxyacetone, such as perfumes, and it is the other ingredients that are probably responsible for a number of cases of eczematous contact dermatitis that have been noted (though not yet reported) by practicing physicians. Whether the risk of allergic reactions is greater with any of the tanning preparations than with other cosmetics is unknown.

Dihydroxyacetone is by no means new to medicine. It has been used as a respiratory stimulant; it has been administered parenterally for cyanide poisoning; it was at one time used experimentally in the treatment of glycogen storage disease. Until recently, however, nothing was known about its local action on the skin, and how it produces pigment is still a matter of surmise. The chemical has no effect on mucous membrane, but it may discolor hair. Some users find that it soils their clothing, especially after prolonged use. Unlike a genuine sun-

tan, the color produced by dihydroxyacetone is not protective against exposure to sunlight, and persons with a deep chemical tan can get a severe sunburn. Cosmetic preparations containing protectants against sunburn in addition to dihydroxyacetone are now being marketed. Dihydroxyacetone is being tried in dermatology for pigmenting white spots (leukoderma). It does not eliminate the need for cosmetic covering materials, but it does make the white spots less evident.

A four-ounce bottle of Man-Tan costs about $3; it is also available in eight-ounce size, costing about $5.

HOT WEATHER STABILITY OF ANTIBIOTICS

When the physician keeps his medical bag in the trunk compartment of his car during the summer months to guard against theft, he may be risking serious deterioration of some of the antibiotic preparations he carries. The expiration dates on antibiotic packages assure maintenance of potency for the indicated periods at the recommended storage temperatures, generally below 80°F., but the temperature in the glove or trunk compartment of a car which has been exposed to summer sunshine may go above 120°F. At such temperatures, it must be assumed that all antibiotic suspensions and solutions, parenteral and oral, will deteriorate rapidly. Procaine penicillin is subject to very rapid decomposition at temperatures above the critical point of 132°F.

DRY PREPARATIONS - Powdered antibiotics which are mixed with water before they are used are more stable than packaged suspensions or solutions, but even with these, and with antibiotic tablets and capsules, deterioration is a problem at high temperatures.

The consistency of antibiotic ointments as well as of other ointments may be affected by heat. If temperatures go high enough to liquefy an antibiotic ointment, settling of the antibiotic may occur, with consequent lack of uniformity when the vehicle resolidifies. In general, if liquefaction has occurred, the ointment should not be used.

CHANGE IN APPEARANCE - A change in the color of an antibiotic solution or the appearance of turbidity generally indicates breakdown, and the preparation should, of course, be discarded. Frequently, however, there will be no change in appearance to warn of deterioration. Where summer heat offers a storage problem, therefore, the quantities of antibiotics kept in the bag should be minimal. If the bag must be left in a car compartment at high temperatures much of the time, fresh antibiotic suspensions and solutions should be substituted for preparations which have been in the bag for more than a week.

At ordinary room temperatures (below 80°F.) most antibiotics, parenteral and oral, liquid and dry, maintain their potency for at least a year or two. Where room temperatures tend to go higher, storage in a refrigerator is desirable. Freezing temperatures may physically alter oral and parenteral aqueous suspensions but generally do not affect their potency. Some ampules are also likely to crack below the freezing point.

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